

University of Groningen

Improving antibacterial prescribing safety in the management of COPD exacerbations

Wang, Yuanyuan; Bahar, Muh. Akbar; Jansen, Anouk M. E.; Kocks, Janwillem W. H.; Alffenaar, Jan-Willem C.; Hak, Eelko; Wilffert, Bob; Borgsteede, Sander D.

Published in:
Journal of Antimicrobial Chemotherapy

DOI:
[10.1093/jac/dkz221](https://doi.org/10.1093/jac/dkz221)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wang, Y., Bahar, M. A., Jansen, A. M. E., Kocks, J. W. H., Alffenaar, J-W. C., Hak, E., Wilffert, B., & Borgsteede, S. D. (2019). Improving antibacterial prescribing safety in the management of COPD exacerbations: systematic review of observational and clinical studies on potential drug interactions associated with frequently prescribed antibacterials among COPD patients. *Journal of Antimicrobial Chemotherapy*, 74(10), 2848-2864. <https://doi.org/10.1093/jac/dkz221>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).



The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy


If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Improving antibacterial prescribing safety in the management of COPD exacerbations: systematic review of observational and clinical studies on potential drug interactions associated with frequently prescribed antibacterials among COPD patients

Yuanyuan Wang ^{1*†}, Muh. Akbar Bahar^{1,2†}, Anouk M. E. Jansen¹, Janwillem W. H. Kocks³, Jan-Willem C. Alffenaar ^{4,5}, Eelko Hak¹, Bob Wilffert^{1,4} and Sander D. Borgsteede^{6,7}

¹Department of PharmacoTherapy, -Epidemiology & -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; ²Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia; ³Department of General Practice and Elderly Care Medicine, Groningen Research Institute for Asthma and COPD, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁴Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁵Faculty of Medicine and Health, School of Pharmacy and Westmead Hospital, University of Sydney, Sydney, Australia; ⁶Department of Clinical Decision Support, Health Base Foundation, Houten, The Netherlands; ⁷Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

*Corresponding author. Unit of PharmacoTherapy, -Epidemiology & -Economics (PTEE), Groningen Research Institute of Pharmacy, University of Groningen, P.O. Box 196, 9700 AD Groningen, The Netherlands. Tel: +31(0)50-363-9163; Fax: +31(0)50-363-2772; E-mail: yuanyuan.wang@rug.nl or yuanyuanwang.research@gmail.com;  orcid.org/0000-0002-5066-1654

†These authors made an equal contribution.

Received 17 September 2018; returned 21 November 2018; revised 13 April 2019; accepted 26 April 2019

Background: Guidelines advise the use of antibacterials (ABs) in the management of COPD exacerbations. COPD patients often have multiple comorbidities, such as diabetes mellitus and cardiac diseases, leading to poly-pharmacy. Consequently, drug–drug interactions (DDIs) may frequently occur, and may cause serious adverse events and treatment failure.

Objectives: (i) To review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies. (ii) To improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD.

Methods: We conducted a systematic review by searching PubMed and Embase up to 8 February 2018 for clinical trials, cohort and case–control studies reporting DDIs of ABs used for COPD. Study design, subjects, sample size, pharmacological mechanism of DDI and effect of interaction were extracted. We evaluated levels of DDIs and quality of evidence according to established criteria and structured the data by possible comorbidities.

Results: In all, 318 articles were eligible for review, describing a wide range of drugs used for comorbidities and their potential DDIs with ABs. DDIs between ABs and co-administered drugs could be subdivided into: (i) co-administered drugs altering the pharmacokinetics of ABs; and (ii) ABs interfering with the pharmacokinetics of co-administered drugs. The DDIs could lead to therapeutic failures or toxicities.

Conclusions: DDIs related to ABs with clinical significance may involve a wide range of indicated drugs to treat comorbidities in COPD. The evidence presented can support (computer-supported) decision-making by health practitioners when prescribing ABs during COPD exacerbations in the case of co-medication.

Introduction

COPD is a complex respiratory disorder characterized by persistent respiratory symptoms and airflow limitation.¹ The chronic and progressive course of COPD is frequently aggravated by exacerbation, defined as an acute worsening of respiratory symptoms, such as

increased cough, dyspnoea and production of sputum.² Exacerbations of COPD can be triggered by respiratory tract infections; 40%–60% of exacerbations are caused by bacteria, especially *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*.³ Evidence from randomized controlled trials

indicated that use of antibacterials (ABs) may reduce the frequency and severity of COPD exacerbations.^{4–6} Therefore, guidelines have recommended involving ABs in the therapeutic and preventive management of COPD exacerbations.^{1,7}

Patients with COPD often suffer from multiple morbidities.⁸ Hence, polypharmacy is common and contributes to drug–drug interactions (DDIs). Adverse drug reactions (ADRs) or therapeutic failure may be the result of interactions between ABs and co-administered drugs. In addition, COPD is an age-related disease and the elderly are more susceptible to the effect of DDIs because of gradual physiological changes affecting pharmacokinetics and pharmacodynamics.⁹

The objectives of this study were to: (i) systematically review DDIs related to frequently prescribed ABs among COPD patients from observational and clinical studies; and (ii) improve AB prescribing safety in clinical practice by structuring DDIs according to comorbidities of COPD. Studies without comparison groups, and therefore with low quality of the causal evidence, such as case reports about QT-interval prolonging interactions, are not included in this review. A DDI handbook such as *Stockley's Drug Interactions* and the official product information should be referred to for the clinical impact of these kinds of interaction.

Methods

Search strategy

We conducted a systematic review following the PRISMA guideline. PubMed and Embase databases were searched for related articles published in English up to 8 February 2018 using key terms 'drug interactions', 'pharmacokinetics' and 'pharmacodynamics', and a list of most frequently used ABs for COPD (Table 1). The ABs were selected based on two related Cochrane reviews and their prescription frequency in the University of Groningen prescription database IADB.nl (<http://www.iadb.nl/>) covering drug prescriptions for ~700 000 people.^{4,5} Additionally, we checked the primary sources of signals from Dutch DDI alert systems: G-Standard and Pharmabase.¹⁰ Reference lists from eligible studies were also tracked for additional qualified papers. Full search details are provided in the [Supplementary data](#), available at JAC Online.

Study selection criteria

Eligible studies met the following criteria: (i) DDIs in humans; (ii) involving the targeted ABs; and (iii) being clinical trials, randomized controlled trials or cohort or case–control studies. We excluded case reports and other

descriptive studies. We further excluded studies with subjects whose pharmacokinetics and pharmacodynamics were not comparable to those of general COPD patients, e.g. newborn babies, pregnant women and patients with severe renal/hepatic impairment. Other exclusion criteria were: (i) unregistered drugs (by FDA or EMA); (ii) involving three or more drug interactions; and (iii) not DDIs (food–drug or gene–drug interactions); (iv) not original studies (reviews, letters and editorials). Pharmacodynamic interactions were beyond the scope of this review and were excluded.

Data extraction and quality assessment

All records were exported to Refworks; titles and abstracts were screened by Y. W. and A. M. E. J. independently. Full-text papers were obtained for records that were considered of potential relevance by at least one of the reviewers. Final decisions were made by consensus between two reviewers according to the preset criteria. Discrepancies between reviewers were resolved by discussion; a third reviewer (E. H.) was asked if no consensus was reached. Information about names of ABs and related interacting drugs, study design, study subjects, sample size, interacting mechanism, effects of interaction and recommendation by study authors were extracted by the same reviewers (Y. W. and A. M. E. J.) and checked by another reviewer (M. A. B.). Quality of evidence was evaluated by grading 0–4 based on criteria (Table 2) used by previous studies.^{11,12}

The strengths of the DDIs were classified into four levels (1, strong; 2, substantial; 3, moderate; 4, weak/no) according to preset published criteria (Table 3).¹² In the cases of several studies on the same DDI combination, we categorized the DDI based on the highest level of severity. Considering that drugs with a narrow therapeutic index (NTI) are more vulnerable to DDIs, the strength of the DDI for such drugs was upgraded one level.¹²

Results

Publications identified by literature search

Our search yielded 1412 and 1734 studies from PubMed and Embase, respectively (Figure 1). After removing duplicates, 2560 articles were screened by title and abstract, of which 630 papers were included for full-text screening, resulting in 282 eligible articles. With 36 studies identified from other resources, we finally obtained 318 studies for assessment in this review.

The interacting drugs, underlying mechanisms, levels and practice recommendations for the DDIs are presented in Table 4. Details on individual studies of DDIs with a potential clinical significance (levels 1–3) are presented in Tables S1 and S2 and the data on studies with a low level of DDIs (weak or no interaction) are presented in Table S3.

Table 1. ABs included in the study that are frequently prescribed among COPD patients^a

Category	Sub-category	ABs included
β-Lactam	penicillin	amoxicillin/clavulanic acid (co-amoxiclav), amoxicillin, flucloxacillin, pheneticillin, phenoxymethylpenicillin (penicillin V)
	cephalosporin	cefaclor, cefuroxime, ceftriaxone, cefradine, ceftazidime
Macrolide		erythromycin, clarithromycin, azithromycin, roxithromycin, clindamycin
Tetracycline		tetracycline, doxycycline, minocycline
Quinolone	fluoroquinolone	ciprofloxacin, moxifloxacin, levofloxacin, ofloxacin, norfloxacin
	other quinolone	pipemidic acid
Sulphonamide		sulfamethoxazole
Others		nitrofurantoin, methenamine, trimethoprim

^aBased on two Cochrane reviews^{4,5} and use within the University of Groningen (the Netherlands) prescription database, IADB.nl (<http://www.iadb.nl/>).

Table 2. Quality of evidence for DDIs^{11,12}

Definition	Score
Clinical research with appropriate control group and relevant pharmacokinetics and/or pharmacodynamic parameters. The studies meet all of the criteria below: <ul style="list-style-type: none"> • The interacting effect of concomitant medication with investigated drugs is reported in the manuscript. • All potential confounders are mentioned and taken into account (for example smoking behaviour or renal function). • The results of interaction are based on the steady-state kinetics. • Variation in dose was adjusted. 	4
Clinical research with appropriate control group and relevant pharmacokinetics and/or pharmacodynamic parameters that does not meet one or more of the pre-defined criteria above.	3
Complete observational studies with clinically relevant results.	2
Incomplete observational studies. (e.g. without controlling confounders or presence of other explanatory factors for the adverse reaction), case reports, summary of product characteristics.	1
<i>In vitro</i> studies, <i>in vivo</i> animal studies, prediction modelling studies.	0

Table 3. Description of level of DDIs¹⁰

Definition	AUC	Clearance	Score ^a
Involved inhibitor	>200% ↑	↓ >67%	1
Involved inducer	>90% ↓	↑ ≥900%	1
For observational studies, RR/OR ≥10			1
Involved inhibitor	75%–200% ↑	↓ ≥43% to <67%	2
Involved inducer	60%–90% ↓	↑ ≥150% to <900%	2
For observational studies, RR/OR 3–9			2
Involved inhibitor	25%–75% ↑	↓ ≥20% to <43%	3
Involved inducer	25%–60% ↓	↑ ≥33% to <150%	3
For observational studies, RR/OR 1.5–2.9			3
Involved inducer/inhibitor	<25% change	↓ <20% or ↑ <33%	4
For observational studies, RR/OR <1.5			4
(a) For interacting drugs with an NTI, the degree of DDIs will be improved to the level one higher			exception
(b) If the DDI level cannot be judged by the above criteria, we assessed it by discussion based on available data and evidence			exception

RR, relative risk; OR, odds ratio; ↑, increase; ↓, decrease.

^a1, strong interaction; 2, substantial interaction; 3, moderate interaction; and 4, weak/no interaction.

We present a step-by-step approach to AB prescribing in COPD: (i) check whether co-morbidity is present; (ii) a quick overview of the AB and its interacting medication, possible interaction mechanism, level of interaction, and practical recommendations is provided in Table 4; and (iii) detailed explanation about related interacting mechanisms and recommendations for the management of related DDIs are provided in the main text.

Mechanisms of DDI

An AB can act as an inhibitor/inducer and/or a substrate, producing moderate to strong DDI with other co-administered medication. There are two scenarios: (i) the co-administered drug alters the pharmacokinetic parameters of the AB; and (ii) the AB influences the pharmacokinetic parameters of the co-administered medication. The main mechanisms of these DDIs are complex formation, inhibition/induction of drug-metabolizing enzymes and alteration

of drug transporters (Table 4). The ability to inhibit CYP3A4 makes ABs prone to interaction with many different drugs as CYP3A4 metabolizes >50% of clinically prescribed drugs.¹³

Information structured according to drugs for comorbidities

The presentation of information on potential clinically significant DDIs with a moderate to strong level of interaction is according to the most frequent comorbidities that have been reported in COPD patients.^{8,14} Potential mechanisms of DDIs and actionable recommendations to manage the DDIs are provided in Table 4.

Diabetes

Patients with COPD have a 50% higher risk of developing diabetes than persons without COPD.¹⁵ Some antidiabetic drugs are

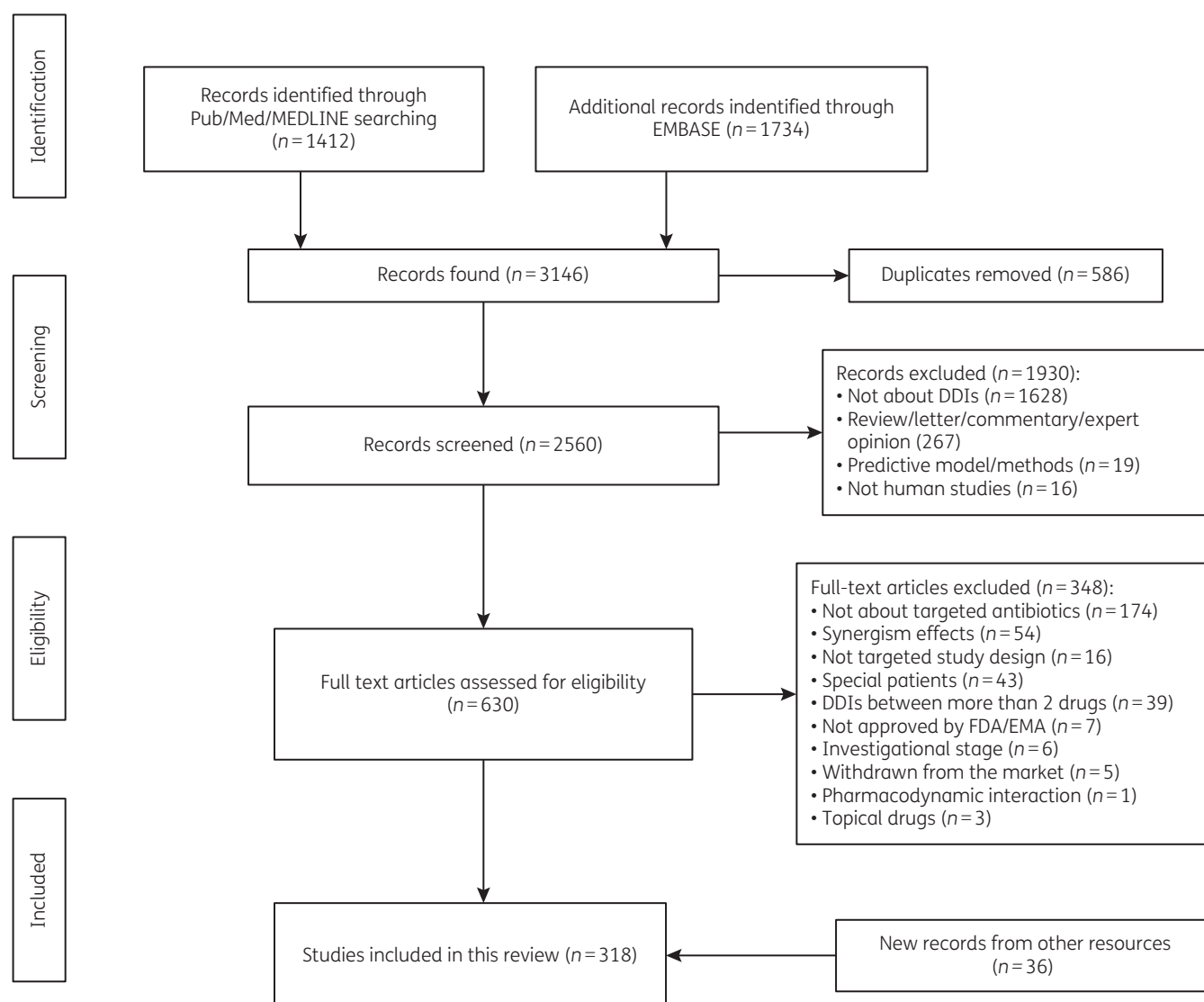


Figure 1. Flow chart of study selection.

substrates of enzymes such as CYP3A4 (glipizide, tolbutamide), CYP2C9 (glipizide, glyburide) and CYP2C8 (repaglinide), and substrates of drug transporter-like P-glycoprotein (P-gp) transporter (glipizide, glyburide).^{16–26} ABs such as clarithromycin (CYP3A4 and P-gp inhibitor), trimethoprim/sulfamethoxazole (CYP2C8/2C9 inhibitor) and levofloxacin (P-gp inhibitor) may inhibit the function of these metabolic enzymes and transporters. These ABs can potentially increase the blood concentration of the antidiabetic agents mentioned above.^{16–26} Consequently, patients may develop hypoglycaemia. Therefore, it is suggested that these combinations should be avoided by substituting a related AB or adjusting the dose of antidiabetic agents as well as monitoring the patients' blood glucose.

Heart and circulatory system diseases

Antihypertensive agents. Hypertension is associated with COPD with a relative risk of 1.6.¹⁵ Antihypertensive calcium channel

blockers (CCBs) such as diltiazem and verapamil are CYP3A4 substrates.^{27–29} Therefore, macrolides (CYP3A4 inhibitors) can enhance the pharmacological activity of CCBs.³⁰ Avoiding the combination by replacement of macrolides or CCBs with another group of drugs or adjusting the dose of CCBs while monitoring blood pressure is recommended. Erythromycin and clarithromycin are the most potent CYP3A4 inhibitors, while azithromycin and roxithromycin are weak inhibitors.^{30,31} Hence, if prescribing macrolides, choosing macrolides with minimal inhibitory capacity to be co-prescribed with CCBs may minimize the risk of DDI.

Spironolactone, a potassium-sparing diuretic, is used to lower blood pressure. Combination of spironolactone with trimethoprim/sulfamethoxazole may produce hyperkalaemia because both drugs can inhibit renal excretion of potassium.³² Therefore, avoiding this combination (by selecting an alternative AB) or adjusting the dose of spironolactone and closely monitoring potassium plasma levels is strongly recommended.

Table 4. DDIs of antibacterials (ABs) for COPD exacerbation and other drugs for treating its comorbidities

Comorbidity	Medication	Interacting AB	Mechanism	Management suggestions	Level of interaction ^a	Reference
Diabetes Antidiabetic medication	glipizide, glyburide glyburide	TMP/SMX clarithromycin	Inhibition of CYP2C9. Inhibition of P-gp.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring patient's blood glucose.	2	16-19
	glipizide, glyburide tolbutamide	levofloxacin clarithromycin TMP/SMX	Inhibition of P-gp. Inhibition of CYP3A4 and P-gp. Inhibition of CYP2C9.	Monitor patient's blood glucose and if necessary adjust dose of substrate.	3	16,20-26
	glipizide, repaglinide repaglinide, rosiglitazone metformin	clarithromycin TMP/SMX TMP/SMX	Inhibition of CYP3A4. Inhibition of CYP2C8. Inhibition of OCT2 and MATE1.			
	Heart and circulatory system diseases Antihypertensive agents	TMP/SMX	Inhibition of potassium secretion.	Avoid combination or adjust dose of substrates and closely monitor potassium plasma levels.	1	32
Lipid-lowering drugs	calcium channel blocker	erythromycin, clarithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	27-29
		azithromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	27
	simvastatin	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	34
	atorvastatin	clarithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	35
Oral anticoagulants	rosuvastatin/pravastatin/ fluvastatin	erythromycin clarithromycin	Inhibition of CYP3A4. Inhibition of OAT.	Monitor side effects and if necessary adjust dose of substrate.	3	36,204
	warfarin, phenprocoumon /acenocoumarol	TMP/SMX	Inhibition of CYP2C9.	Avoid combination or closely monitor the change of INR routinely and adjust dose if needed.	1	39-58
		amoxicillin/co- amoxiclav, ceftriaxone clarithromycin, azithro- mycin, ciprofloxacin, levofloxacin, ofloxacin, doxycycline	Alterations in normal gut flora. Inhibition of CYP3A4 or alterations in normal gut flora.	Choose alternative AB or, if not possible, monitor the change of INR routinely.	2	
	edoxaban, dabigatran, rivaroxaban	erythromycin, clarithromycin	Inhibition of CYP3A4 and/or P-gp.	Consider alternative or adjusted dose of substrate or monitor signs of excessive anticoagulant effect.	2	62,63
	warfarin	moxifloxacin	Inhibition of CYP3A4 or alterations in normal gut flora.	Monitor the change of INR routinely.	3	41

Antiarrhythmic agents	digoxin	clarithromycin	Inhibition of P-gp.	Avoid combination or perform TDM and if necessary adjust dose of substrate.	1	68-71
	quinidine, lignocaine procainamide	erythromycin TMP	Inhibition of CYP3A4. Inhibition of tubular secretion.	Consider alternative or perform TDM and if necessary adjust dose of substrate.	2	64-67
	pindolol, digoxin procainamide	TMP/SMX levofloxacin, ofloxacin	Inhibition of tubular secretion. Inhibition of OCT.	Perform TDM and if necessary adjust dose of substrate.	3	72-75
Respiratory diseases Medication for obstructive airways diseases	methylprednisolone, montelukast theophylline	clarithromycin	Inhibition of CYP3A4 and P-gp.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects. For theophylline, perform TDM.	2	78-85,90-97
	loratadine	erythromycin ciprofloxacin erythromycin, clarithromycin	Inhibition of CYP3A4. Inhibition of CYP1A2. Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	86,87
	roflumilast rifabutin rifampicin, rifabutin rifampicin, rifabutin rifampicin	erythromycin clarithromycin clarithromycin TMP/SMX, doxycycline TMP/SMX moxifloxacin	Inhibition of CYP3A4. Inhibition of CYP3A4. Induction of CYP3A4. Induction of CYP3A4/CYP2C9. Inhibition of mixed oxidases. Induction of phase II enzymes.	Avoid combination. Consider alternative AB for COPD Consider alternative AB for COPD or monitor the effectiveness of AB and if necessary adjust dose of AB.	1 2 3	101,110,111 100,101 102-104,106-109
Neurological disorders Anti-Parkinson's agents	bromocriptine	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	112
	cabergoline	clarithromycin	Inhibition of CYP3A4 and P-gp.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	113
	carbamazepine, phenytoin carbamazepine phenytoin phenobarbital	doxycycline ciprofloxacin TMP/SMX doxycycline	Induction of CYP3A4. Inhibition of CYP3A4/1A2. Inhibition of CYP2C8. Induction of CYP3A4.	Consider alternative or perform TDM. Consider alternative or perform TDM. Consider alternative or perform TDM. Monitor side effects and if necessary adjust dose of substrate.	2 2 2 3	116,117 118 116,119 115
Depression and psychiatric disorders Antidepressant, anxiolytic and anti-psychotic agents	buspirone	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	125
	quetiapine pimozide, trazodone clozapine	erythromycin clarithromycin ciprofloxacin	Inhibition of CYP3A4. Inhibition of CYP3A4. Inhibition of CYP1A2.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects. For clozapine, perform TDM.	2	122-124,129
	diazepam	ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust the dose of substrate.	3	127
Dyspepsia Antidyspepsia medications	aluminium hydroxide, sucralfate lansoprazole	quinolone, tetracyclines clarithromycin	Complex formation. Inhibition of CYP3A4.	Avoid combination or administer quinolone at least 2 h before or 6 h after co-agents. Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	1 2	131-142 147

Continued

Table 4. Continued

Comorbidity	Medication	Interacting AB	Mechanism	Management suggestions	Level of interaction ^a	Reference
HIV Anti-HIV drugs	calcium carbonate	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	131,139
	bismuth subsalicylate	quinolone, tetracyclines	Complex formation.	Administration interval of at least 2 h.	3	143,205
	didanosine	ciprofloxacin	Complex formation.	Avoid combination or administer quinolone at least 2 h before or 6 h after co-agents.	1	149,150
	saquinavir	erythromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	151
Other Pulmonary arterial hypertension medications	lamivudine, didanosine	TMP/SMX	Inhibition of tubular secretion.	Monitor side effects and if necessary adjust dose of substrate.	3	152,153
	bosentan	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	206
	ambrisentan	clarithromycin	Inhibition of CYP3A4 and P-gp.	Monitor side effects and if necessary adjust dose of substrate.	3	207
	brotizolam, triazolam, zopiclone, zolpidem	erythromycin	Inhibition of CYP3A4.	Consider an alternative AB or other hypnotic drugs (not a CYP3A4 substrate).	2	208-210
Insomnia medications		ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and if necessary choose alternative AB or other hypnotic drugs (not a CYP3A4 substrate).	3	211
Antifungal agents	voriconazole	erythromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects. For voriconazole, perform TDM and adjust dose if needed.	2	154,155
	itraconazole	ciprofloxacin	Inhibition of CYP3A4.			
Antineoplastic drugs	vinorelbine	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	179
Anti-gout drugs	colchicine	clarithromycin	Inhibition of CYP3A4.	Avoid combination or perform TDM and adjust dose if needed.	1	180
Anaesthesia drugs		azithromycin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate or use cautiously by monitoring side effects.	2	180
	probenecid	ciprofloxacin	Inhibition of OAT.	Monitor side effects and if necessary adjust dose of substrate.	3	194,195
	midazolam	clarithromycin, erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	156-160
	ketamine	clarithromycin	Inhibition of CYP3A4.	Consider alternative or perform TDM and adjust dose if needed.	2	161
	alfentanil	erythromycin	Inhibition of CYP3A4.	Monitor side effects and if necessary adjust dose of substrate.	3	162-166
	ropivacaine	clarithromycin	Inhibition of CYP3A4.			
		ciprofloxacin	Inhibition of CYP1A2.			
	midazolam	roxithromycin	Inhibition of CYP3A4.			

<i>Analgesics</i>	oxycodone	clarithromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	167
<i>Immunosuppressant drugs</i>	cyclosporine everolimus	erythromycin erythromycin	Inhibition of CYP3A4. Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and perform TDM.	1	168,169,181,182
	tacrolimus	levofloxacin	Inhibition of CYP3A4 or P-gp.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	170
	cyclosporine	ciprofloxacin	Inhibition of CYP3A4.	Monitor side effects and, if necessary adjust dose of substrate.	3	171,172
<i>Vasoactive agents</i>	sildenafil	clarithromycin, erythromycin, ciprofloxacin	Inhibition of CYP3A4.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	173,174
<i>Appetite suppressants</i>	sibutramine	clarithromycin	Inhibition of CYP3A4 and P-gp.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	175,176
<i>Emergency birth control</i>	ulipristal acetate	erythromycin	Inhibition of CYP3A4.	Avoid combination or adjust dose of substrates and closely monitor side effects.	1	178
<i>Antimalarial agents</i>	halofantrine	tetracycline	Probably by CYP3A4 inhibition.	Avoid combination or perform TDM and adjust dose if needed.	1	177
<i>Muscle relaxants</i>	tizanidine	ciprofloxacin	Inhibition of CYP1A2.	Avoid combination or perform TDM and adjust dose if needed.	1	183
<i>Anti-diarrhoeals</i>	loperamide	TMP/SMX	Inhibition of CYP2C8.	Consider alternative or adjusted dose of substrate, or use cautiously by monitoring side effects.	2	186
<i>Anaemia medications</i>	iron supplements	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	212-220
<i>Other metal cations</i>	zinc sulfate	quinolone, tetracyclines	Complex formation.	Avoid co-administration or administer at interval of at least 2 h.	2	144,188,189
	calcium acetate, calcium carbonate, calcium polycarbophil, patiromer, lanthanum carbonate, sevelamer	quinolone, tetracyclines	Complex formation.	Administer at interval of at least 2 h.	3	139,190-193
<i>Other ABs</i>	linezolid	clarithromycin	Inhibition of P-gp.	Consider alternative or perform TDM and adjust dose if needed.	2	196
	dapsone	trimethoprim	Inhibition of CYP2C8.	Monitor side effects and if necessary adjust dose of substrate.	3	187
	neomycin	penicillin V	NA	Consider alternative or adjust dose of penicillin.	3	221

All detailed supporting information about each DDI is available in Tables [S1](#) and [S2](#).

OCT, organic cation transporter; OAT, organic anion transporter; MATE1, multidrug and toxin extrusion 1; TMP/SMX, trimethoprim/sulfamethoxazole; NA, not available yet.
^a1, strong interaction; 2, substantial interaction; 3, moderate interaction; 4, weak or no interaction.

Lipid-lowering drugs. Lipid metabolism problems are among the most prevalent comorbidities in COPD patients.¹⁴ The main pharmacological approach to the management of blood cholesterol levels is statin therapy.³³ Some ABs increase the plasma concentration of statins by several mechanisms. Statins such as simvastatin and atorvastatin are biodegraded by CYP3A4.^{34,35} Therefore, potent CYP3A4 inhibitors (erythromycin and clarithromycin) increase the risk of statin-related side effects such as rhabdomyolysis.^{34,35} Other statins, such as rosuvastatin, pravastatin and fluvastatin, are not CYP3A4 substrates.³⁶ However, the hepatic clearance of these statins is facilitated by anion-transporting polypeptides.³⁷ These influx transporters facilitate the transport of statins from systemic blood to liver cells to be metabolized or subsequently delivered into the bile for elimination.³⁷ Clarithromycin and erythromycin have been reported to be inhibitors of these transporters.³⁸ Therefore, replacing erythromycin and clarithromycin with other ABs, temporarily stopping statins or adjusting the dose of statins while monitoring statin-related side effects is recommended.

Oral anticoagulants. Both coumarins and direct oral anticoagulants (DOACs) may interact with ABs. Multiple studies reported that DDIs between ABs and coumarins (warfarin, phenprocoumon, acenocoumarol) led to increased risks of haemorrhage.^{39–58} Several interaction mechanisms were proposed.^{59,60} One mechanism is by disruption of intestinal flora that synthesizes vitamin K, as many ABs could alter the balance of gut flora.⁵⁹ Another mechanism is that ABs (e.g. trimethoprim/sulfamethoxazole and macrolides) alter coumarin metabolism, which mainly involves CYP2C9 (trimethoprim/sulfamethoxazole) and CYP3A4 (macrolides).⁶⁰ Therefore, to choose alternative ABs or, if not possible, to monitor international normalized ratio (INR) values and adjust the dose of coumarins is recommended.

DOACs are regarded as a safe alternative to replace coumarins.⁶¹ However, since some DOACs (edoxaban, rivaroxaban, dabigatran) are substrates of CYP3A4 and/or the P-gp transporter, their AUC values can be increased by ABs such as macrolides.^{62,63} Therefore, when macrolides and DOACs are required in combination, careful monitoring of signs of bleeding is needed, and adjusting the dose of DOACs should be done if necessary.

Antiarrhythmic agents. Some antiarrhythmic agents, such as digoxin, quinidine, lignocaine and procainamide, potentially interact with ABs.^{64–75} Quinidine and lignocaine are CYP3A4 substrates and therefore macrolides may inhibit their degradation and increase their bioavailabilities.^{64,65} The renal clearance of procainamide and digoxin is inhibited by trimethoprim.^{66,67,72,73} The mechanism of interaction is inhibition of tubular secretion via inhibition of the renal organic cation transporter because they are substrates of the transporter.^{66,67,72,73} Consequently, blood concentrations of these drugs are increased.^{66,67,72,73} Digoxin is a substrate of the P-gp transporter.^{68–71} Clarithromycin could elevate the AUC of digoxin, which may cause toxicities.^{68–71} Since quinidine, lignocaine, digoxin and procainamide are drugs with an NTI, avoiding ABs that can lead to DDIs with these drugs is recommended.^{76,77} However, if their co-prescription is necessary, therapeutic drug monitoring (TDM) of these antiarrhythmic agents is strongly recommended.⁷⁷

Respiratory diseases

Medication for obstructive airways diseases

One of the most prevalent comorbidities in COPD is asthma.¹⁴ Some anti-asthma drugs, such as methylprednisolone, montelukast, loratadine, roflumilast and theophylline, are substrates of CYP3A4 and/or the P-gp transporter and have been shown to interact with macrolides.^{78–87} Hence, one might consider other ABs for combination with asthma drugs, or closely monitor patients, especially in the case of theophylline, which is an NTI drug.⁸⁸ As theophylline is also metabolized by CYP1A2,⁸⁹ ciprofloxacin (a CYP1A2 potent inhibitor) should be avoided.^{90–97}

Antimycobacterial agents

Tuberculosis and COPD share comparable risk factors and therefore can co-occur in individuals, particularly elderly patients.⁹⁸ Rifampicin and rifabutin (antimycobacterial agents) work as potent inducers of hepatic and intestinal CYP enzymes.⁹⁹ They can markedly reduce the activities of clarithromycin, doxycycline and trimethoprim/sulfamethoxazole by causing their rapid elimination.^{100–104} Since rifampicin also exhibits other AB properties, such as activity against MRSA in combination with other drugs, rationalizing antimicrobial therapy should be considered accordingly.¹⁰⁵ Alternative ABs for treating COPD are also recommended to reduce the risk of treatment failures.

Moxifloxacin might be an alternative AB for clarithromycin, doxycycline and trimethoprim/sulfamethoxazole owing to its moderate or weak interaction with rifampicin.^{106–109} Moxifloxacin is not metabolized by CYP450 and its interacting mechanisms with rifampicin might be facilitated by induction of other enzymes, such as uridine diphosphate-glucuronosyltransferases and sulfotransferases.^{106–109}

Rifabutin and rifampicin are CYP substrates. Rifabutin is a CYP3A4 substrate, and therefore macrolides may increase its serum concentration and enhance the risk of related ADR.^{101,110,111} Another study reported that rifampicin concentrations in blood are moderately elevated by co-trimoxazole.¹⁰⁴ It was assumed that the interaction was facilitated by inhibition of mixed-function oxidases, which are responsible for metabolizing rifampicin.¹⁰⁴ Thus, considering alternative ABs or monitoring the clinical and biochemical parameters for rifampicin-related hepatotoxicity is suggested when rifampicin and co-trimoxazole are combined.

It should be mentioned that not all the drugs for atypical *Mycobacterium* spp. were included in this review because selection was limited to ABs that are used frequently among COPD patients. For drugs outside the scope of this review, other references (e.g. statements of product characteristics) need to be considered.

Neurological disorders

Anti-Parkinson's drugs

Bromocriptine and cabergoline (dopamine agonists) are substrates of CYP3A4 and/or the P-gp transporter.^{112,113} Co-prescription of these drugs with clarithromycin and erythromycin may produce major interactions and therefore might lead to toxicities.^{112,113} Thus, avoiding such combinations is recommended. However,

if this is not possible, adjusting the dose of these Parkinson's medications and closely monitoring side effects are needed.

Antiepileptic drugs

Carbamazepine, phenytoin and phenobarbital can stimulate the activity of a variety of CYP (CYP1A2/2C9/3A4) and glucuronyl transferase enzymes, which results in multiple DDIs with other substrates for these enzymes.^{114–116} Carbamazepine and phenytoin were reported to reduce the half-life of doxycycline by stimulating the hepatic metabolism of doxycycline.¹¹⁷ It is suggested that an alternative AB should be considered or that the dose of antiepileptic drugs should be adjusted while monitoring the AB activity of doxycycline.

Carbamazepine and phenytoin are substrates of CYP1A2/3A4 and CYP2C8, respectively. A CYP1A2/3A4 inhibitor (ciprofloxacin) and a CYP2C8 inhibitor (trimethoprim) were reported to increase the bioavailability of carbamazepine and phenytoin, respectively.^{116–119} Moreover, phenytoin is an NTI drug and therefore avoiding using trimethoprim concomitantly or performing TDM of phenytoin is recommended when this DDI is not avoidable.¹²⁰

Ciprofloxacin was reported to increase the AUC of carbamazepine by >50%.¹¹⁸ Although it is not clear whether carbamazepine can be considered to be an NTI drug, a rising carbamazepine plasma concentration because of this DDI needs special caution.¹²¹ Dose adjustment and TDM of carbamazepine are suggested to diminish potential toxicities.

Depression and psychiatric disorders

Depression and psychiatric disorders are common among COPD patients.¹⁴ Some antidepressant (trazodone), anxiolytic (buspirone) and antipsychotic (quetiapine, and pimozide) drugs are CYP3A4 substrates and therefore might trigger clinically relevant DDIs with ABs.^{122–125} Erythromycin and clarithromycin increased the AUCs of these drugs substantially.^{122–125} Considering alternative ABs or adjusting the dose of substrates and monitoring related side effects is the way to control potential ADR.

CYP3A4 is also responsible for metabolizing diazepam, in addition to CYP2C19.¹²⁶ Ciprofloxacin was reported to decrease diazepam clearance moderately by inhibiting CYP3A4 activity.¹²⁷ Monitoring diazepam-related side effects can therefore be considered when this combination is prescribed.

Ciprofloxacin is also a potent CYP1A2 inhibitor.¹²⁸ Therefore, metabolism of an atypical antipsychotic, clozapine, a CYP1A2 substrate with an NTI, can be altered by ciprofloxacin, which produces a significant increase in clozapine serum concentration.^{129,130} Replacing ciprofloxacin or TDM of clozapine is an option that can be chosen in managing this DDI.

Dyspepsia

Drugs containing metal cations (e.g. antacids, sucralfate and bismuth salts) produced chemical interactions with some ABs, such as oral tetracyclines (e.g. tetracycline, doxycycline) and fluoroquinolones (e.g. ciprofloxacin, moxifloxacin).^{131–144} Tetracyclines have a strong tendency to form chelates due to their structural features, which include many chelation sites.¹⁴⁵ Meanwhile, fluoroquinolones have two main sites of metal chelation: 4-keto oxygen and 3-carboxylic acid groups.¹⁴⁶

The formation of metal ion chelation complexes decreases absorption of tetracycline and fluoroquinolones, and this reduced bioavailability may lead to ineffectiveness of these ABs.^{131–144} Therefore, it is recommended that their combination should be avoided by replacing tetracyclines and fluoroquinolones with another AB, e.g. amoxicillin or amoxicillin/clavulanic acid. It was reported that antacids did not affect the bioavailability of amoxicillin and amoxicillin/clavulanic acid when they were co-administered.¹³⁶ If replacement of the AB is not possible, replacement of antacids, sucralfate or bismuth salts with a proton pump inhibitor (PPI) is also favoured. Another alternative is to separate administration by using quinolone or tetracycline at least 2 h before or 6 h after the dyspepsia drugs.

When considering a PPI, lansoprazole may not be the best alternative as it is partly metabolized by CYP3A4 and has been found to interact with clarithromycin.¹⁴⁷

HIV

HIV-positive patients have an ~50% higher risk of developing COPD than HIV-negative patients.¹⁴⁸ Thus, the risk of co-prescriptions for treating these chronic conditions may also be high. A protease inhibitor (saquinavir) and NRTIs (didanosine and lamivudine) were found to clinically interact with ABs.^{149–153}

Didanosine is very acid sensitive, and therefore didanosine formulations are supplemented with buffering mixtures containing magnesium hydroxide, dihydroxyaluminium sodium carbonate and sodium citrate to prevent hydrolysis by gastric acid.¹⁴⁹ These metal ions may form chelation complexes with quinolones and reduce their serum concentration.^{149,150} Two studies confirmed the didanosine and ciprofloxacin interaction, and recommended that when co-administration cannot be avoided, ciprofloxacin must be given at least 2 h before didanosine.^{149,150}

Trimethoprim/sulfamethoxazole may inhibit clearances of didanosine and lamivudine by competitively hindering their renal secretion.^{152,153} Consequently, AUCs of didanosine and lamivudine are elevated moderately.^{152,153} Monitoring of the presumed side effects should be performed.

Saquinavir is metabolized by CYP3A4 and the presence of erythromycin increased its AUC by almost 100%.¹⁵¹ Choosing an alternative AB or adjusting the dose of saquinavir while monitoring toxicities can be considered as a means of managing this DDI.

Other potential clinically significant DDIs

Some other drugs that have indications for comorbidities in COPD patients were found to interact with ABs. Some individual drugs of different classes (e.g. voriconazole and vinorelbine) are metabolized by CYP3A4.^{154–182} Therefore, their metabolism is interfered with by CYP3A4 inhibitors (macrolides).^{154–182} Other drugs are CYP1A2 substrates (e.g. ropivacaine and tizanidine) and therefore potent inhibitors of CYP1A2, such as quinolones, significantly alter their metabolism and elevate their bioavailabilities.^{164,183–185} Others are CYP2C8 substrates (e.g. loperamide for diarrhoea) and therefore trimethoprim (a potent CYP2C8 inhibitor) inhibits their clearance and increases their AUC values.^{186,187} Some drugs containing metal cations (e.g. Fe, Zn, Ca) should be avoided or administered with a separation of at least 2 h from quinolones and tetracyclines.^{139,144,188–193} Other interactions were facilitated by

drug transporters. A uricosuric agent (probenecid) interacts moderately with ciprofloxacin via competitive inhibition of organic anion transporters in renal tubules.^{194,195} Moreover, linezolid, which is a substrate of the P-gp transporter, can potentially produce clinically significant interaction with P-gp inhibitors (macrolides).¹⁹⁶

DDIs related to NTIs

Some ABs may interact with NTI drugs and therefore can produce serious ADRs. The NTI drugs in this review include CYP3A4 substrates (theophylline, ketamine, everolimus, tacrolimus, halofantrine, lignocaine, quinidine, voriconazole, carbamazepine, warfarin, cyclosporine, colchicine, phenprocoumon/acenocoumarol); CYP1A2 substrates (theophylline, carbamazepine, clozapine, tizanidine); CYP2C9 substrates and drugs sensitive to alterations in the normal gut flora (warfarin, phenprocoumon/acenocoumarol); a CYP2C8 substrate (phenytoin); substrates of the P-gp transporter (digoxin, linezolid); and a substrate of the organic cation transporter (procainamide).^{76,77,88,120,197}

Discussion

Included articles

This study outlines the possible DDIs related to frequently prescribed ABs in COPD patients from clinical and observational studies. We only included well-designed studies (≥ 2 points) since they provide more valid evidence than studies without a control or comparison group (0 or 1 point). DDIs based on case reports or hypotheses may lead to unnecessary warnings if these are not confirmed by well-designed studies. One classic example of this point is ABs and oral contraceptive interactions; many cases of unintended pregnancies were reported after ABs were prescribed to women on oral contraceptives, which attracted much attention from health practitioners.^{198,199} After scientific evidence from clinical and pharmacokinetic studies has consistently and repeatedly failed to support such interaction, the warning about DDIs between hormonal contraception and non-rifampicin ABs has finally been cancelled in related guidelines.¹⁹⁹

Mechanisms of DDI

A DDI of potential clinical significance between an AB and a co-administered medication may occur in two situations: (i) the co-administered drug influences the absorption, distribution, metabolism and elimination (ADME) of the AB; and (ii) the AB influences the ADME of the co-administered medication. When the AB acted as a substrate, some co-administered drugs reduced the blood concentration of the AB and led to failure of the AB treatment to reduce COPD exacerbations. Other co-administered drugs increased the blood concentration of the AB, which could result in the termination of AB use because of an ADR, and therefore acted against the control of infection. Acting as inhibitors, ABs could also increase the blood concentrations of co-administered drugs, which may also produce an ADR and lead to termination of co-administered drugs, and therefore may lead to failure of treatment of comorbidities. Thus, DDIs related to ABs may hinder effective infection control and exacerbation management among COPD patients as well as treatment of comorbidities in COPD.

Comorbidities among COPD patients

The impact of comorbidities on quality of life in COPD patients is well reported; however, potential drug interactions between drugs for these comorbidities and ABs used for COPD have received little specific attention. From this review, we found that many drugs (e.g. those used for heart and circulatory system diseases) should not be co-administered with related ABs, and other actions are necessary, such as dose adjustment, choosing an alternative drug and monitoring ADRs. These drug interactions may not only influence treatment options for clinical practitioners but also influence treatment effects for both COPD and comorbidities.

Information collected in this review can be used as input to improve the sensitivity and specificity of DDI alert systems. Moreover, this study may also be attractive for researchers in this field who may take into account the availability of high-quality studies when evaluating the evidence for many potential interactions.

Special warning for NTI drugs

We found that some NTI drugs might potentially interact with ABs. Because of the narrow separation between effective and toxic dosing of these drugs, a small alteration of their pharmacokinetic parameters can produce fatal consequences.^{88,120} Therefore, combination with particular ABs that have an ability to inhibit their clearance pathways should be avoided if possible. However, if the benefits of combination outweigh the potential side effects, dose adjustment and performing TDM of the NTI drugs are strongly recommended.

Limitations

Some limitations of this review are worth mentioning. First, although we reviewed a significant part of the literature, we did not include all sources that might indicate relevant DDIs, such as case reports, summary of product characteristics and theoretical hypotheses. As a result, we did not find some DDIs that are considered serious and clinically highly relevant, such as QT-interval prolonging interactions for combinations of macrolides with other QT-prolonging drugs or the risk of pseudotumour cerebri in the case of combinations of doxycycline with vitamin A analogues.^{200,201} Such interactions are commonly found as case reports, as it is unethical to design studies to confirm these serious risks in clinical studies. However, for some DDIs it is possible to study the clinical manifestation of a potential DDI in an observational study using real-world drug utilization data.²⁰² Secondly, selection of the ABs included in this review was based on their frequent use in COPD and therefore information for other ABs used for COPD comorbidities, such as atypical *Mycobacterium* spp., is limited, and this may restrict the scope of application of this review. Thirdly, due to limited comparative analyses for several specific DDIs included in this review, it may be difficult to make recommendations for a specific situation. Our classification of DDI levels only offers a general consideration. The specific impact of a DDI is determined by many variables, such as different doses and formulations and the comorbidities of patients. Therefore, case-by-case analysis is important in clinical practice and a drug interaction handbook such as *Stockley's Drug Interactions*²⁰³ further expands on these issues.

Conclusions

Clinically significant DDIs related to ABs may involve a wide range of indicated drugs to treat comorbidities in COPD. Clinicians should pay attention to these drug interactions when prescribing ABs in order to reduce the frequency and severity of exacerbations in COPD patients and take necessary actions to ensure therapeutic effect and safety of patients. This study may contribute to better prescribing of ABs to COPD patients with comorbidities where potentially interacting drug combinations may be used. Furthermore, the information may highlight gaps in scientific knowledge about potential adverse effects from DDIs.

Funding

This study was supported by internal funding. Y. W. received a scholarship (file number: 201506010259) from China Scholarship Council (CSC; <http://www.csc.edu.cn/>) for her PhD studies at the University of Groningen, Groningen, the Netherlands. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Transparency declarations

None to declare.

Supplementary data

The detailed search terms and Tables S1 to S3 are available as [Supplementary data](#) at JAC Online.

References

- Vogelmeier CF, Criner GJ, Martinez FJ *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017; **195**: 557–82.
- Decramer M, Janssens W, Miravittles M. Chronic obstructive pulmonary disease. *Lancet* 2012; **379**: 1341–51.
- Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359**: 2355–65.
- Vollenweider DJ, Jarrett H, Steurer-Stey CA *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; issue **12**: CD010257.
- Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2013; issue **12**: CD009764.
- Wang Y, Zijp TR, Bahar MA *et al.* Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2018; **73**: 3231–43.
- Wedzicha JA, Calverley PMA, Albert RK *et al.* Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; **50**: 1602265.
- Chetty U, McLean G, Morrison D *et al.* Chronic obstructive pulmonary disease and comorbidities: a large cross-sectional study in primary care. *Br J Gen Pract* 2017; **67**: e321–8.
- Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; **57**: 6–14.
- Bahar MA, Hak E, Bos JH *et al.* The burden and management of cytochrome P450 2D6 (CYP2D6)-mediated drug-drug interaction (DDI): co-medication of metoprolol and paroxetine or fluoxetine in the elderly. *Pharmacoepidemiol Drug Saf* 2017; **26**: 752–65.
- van Roon EN, Flikweert S, le Comte M *et al.* Clinical relevance of drug-drug interactions: a structured assessment procedure. *Drug Saf* 2005; **28**: 1131–9.
- Bahar MA, Setiawan D, Hak E *et al.* Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics* 2017; **18**: 701–39.
- Zhou S, Chan E, Li X *et al.* Clinical outcomes and management of mechanism-based inhibition of cytochrome P450 3A4. *Ther Clin Risk Manag* 2005; **1**: 3–13.
- Divo M, Cote C, de Torres JP *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; **186**: 155–61.
- Mannino DM, Thorn D, Swensen A *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; **32**: 962–9.
- Schelleman H, Bilker WB, Brensinger CM *et al.* Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. *Clin Pharmacol Ther* 2010; **88**: 214–22.
- Lilja JJ, Niemi M, Fredrikson H *et al.* Effects of clarithromycin and grapefruit juice on the pharmacokinetics of glibenclamide. *Br J Clin Pharmacol* 2007; **63**: 732–40.
- Tan A, Holmes HM, Kuo YF *et al.* Coadministration of co-trimoxazole with sulfonylureas: hypoglycemia events and pattern of use. *J Gerontol A Biol Sci Med Sci* 2015; **70**: 247–54.
- Kradjan WA, Witt DM, Opheim KE *et al.* Lack of interaction between glipizide and co-trimoxazole. *J Clin Pharmacol* 1994; **34**: 997–1002.
- Jayasagar G, Dixit AA, Kishan V *et al.* Effect of clarithromycin on the pharmacokinetics of tolbutamide. *Drug Metabol Drug Interact* 2000; **16**: 207–15.
- Wing LM, Miners JO. Cotrimoxazole as an inhibitor of oxidative drug metabolism: effects of trimethoprim and sulphamethoxazole separately and combined on tolbutamide disposition. *Br J Clin Pharmacol* 1985; **20**: 482–5.
- Niemi M, Neuvonen PJ, Kivisto KT. The cytochrome P4503A4 inhibitor clarithromycin increases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2001; **70**: 58–65.
- Niemi M, Kajosaari LI, Neuvonen M *et al.* The CYP2C8 inhibitor trimethoprim increases the plasma concentrations of repaglinide in healthy subjects. *Br J Clin Pharmacol* 2004; **57**: 441–7.
- Hruska MW, Amico JA, Langoe TY *et al.* The effect of trimethoprim on CYP2C8 mediated rosiglitazone metabolism in human liver microsomes and healthy subjects. *Br J Clin Pharmacol* 2005; **59**: 70–9.
- Grun B, Kiessling MK, Burhenne J *et al.* Trimethoprim-metformin interaction and its genetic modulation by OCT2 and MATE1 transporters. *Br J Clin Pharmacol* 2013; **76**: 787–96.
- Muller F, Pontones CA, Renner B *et al.* N(1)-methylnicotinamide as an endogenous probe for drug interactions by renal cation transporters: studies on the metformin-trimethoprim interaction. *Eur J Clin Pharmacol* 2015; **71**: 85–94.
- Wright AJ, Gomes T, Mamdani MM *et al.* The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ* 2011; **183**: 303–7.
- Gandhi S, Fleet JL, Bailey DG *et al.* Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. *JAMA* 2013; **310**: 2544–53.
- Fraser LA, Shariff SZ, McArthur E *et al.* Calcium channel blocker-clarithromycin drug interaction did not increase the risk of nonvertebral fracture: a population-based study. *Ann Pharmacother* 2015; **49**: 185–8.

- 30 Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; **50**: 285–95.
- 31 Yamazaki H, Shimada T. Comparative studies of in vitro inhibition of cytochrome P450 3A4-dependent testosterone 6 β -hydroxylation by roxithromycin and its metabolites, troleandomycin, and erythromycin. *Drug Metab Dispos* 1998; **26**: 1053–7.
- 32 Antoniou T, Hollands S, Macdonald EM *et al*. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. *CMAJ* 2015; **187**: E138–43.
- 33 Parhofer KG. The treatment of disorders of lipid metabolism. *Dtsch Arztebl Int* 2016; **113**: 261–8.
- 34 Kantola T, Kivisto KT, Neuvonen PJ. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64**: 177–82.
- 35 Amsden GW, Kuye O, Wei GC. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; **42**: 444–9.
- 36 Li DQ, Kim R, McArthur E *et al*. Risk of adverse events among older adults following co-prescription of clarithromycin and statins not metabolized by cytochrome P450 3A4. *CMAJ* 2015; **187**: 174–80.
- 37 Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol* 2009; **158**: 693–705.
- 38 Seithel A, Eberl S, Singer K *et al*. The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. *Drug Metab Dispos* 2007; **35**: 779–86.
- 39 Glasheen JJ, Fugit RV, Prochazka AV. The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. *J Gen Intern Med* 2005; **20**: 653–6.
- 40 Lane MA, Zeringue A, McDonald JR. Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. *Am J Med* 2014; **127**: 657.
- 41 Ghaswalla PK, Harpe SE, Tassone D *et al*. Warfarin-antibiotic interactions in older adults of an outpatient anticoagulation clinic. *Am J Geriatr Pharmacother* 2012; **10**: 352–60.
- 42 Mergenhagen KA, Olbrych PM, Mattappallil A *et al*. Effect of azithromycin on anticoagulation-related outcomes in geriatric patients receiving warfarin. *Clin Ther* 2013; **35**: 425–30.
- 43 McCall KL, Anderson HG Jr, Jones AD. Determination of the lack of a drug interaction between azithromycin and warfarin. *Pharmacotherapy* 2004; **24**: 188–94.
- 44 Fischer HD, Juurlink DN, Mamdani MM *et al*. Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med* 2010; **170**: 617–21.
- 45 Washington C, Hou SY, Hughes NC *et al*. Ciprofloxacin prolonged-release tablets do not affect warfarin pharmacokinetics and pharmacodynamics. *J Clin Pharmacol* 2007; **47**: 1320–6.
- 46 Israel DS, Stotka J, Rock W *et al*. Effect of ciprofloxacin on the pharmacokinetics and pharmacodynamics of warfarin. *Clin Infect Dis* 1996; **22**: 251–6.
- 47 Bianco TM, Bussey HI, Farnett LE *et al*. Potential warfarin-ciprofloxacin interaction in patients receiving long-term anticoagulation. *Pharmacotherapy* 1992; **12**: 435–9.
- 48 Abdel-Aziz MI, Ali MA, Hassan AK *et al*. Warfarin-drug interactions: an emphasis on influence of polypharmacy and high doses of amoxicillin/clavulanate. *J Clin Pharmacol* 2016; **56**: 39–46.
- 49 Schelleman H, Bilker WB, Brensinger CM *et al*. Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. *Clin Pharmacol Ther* 2008; **84**: 581–8.
- 50 Baillargeon J, Holmes HM, Lin YL *et al*. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012; **125**: 183–9.
- 51 O'Reilly RA, Motley CH. Racemic warfarin and trimethoprim-sulfamethoxazole interaction in humans. *Ann Intern Med* 1979; **91**: 34–6.
- 52 Mercadal Orfila G, Gracia Garcia B, Leiva Badosa E *et al*. Retrospective assessment of potential interaction between levofloxacin and warfarin. *Pharm World Sci* 2009; **31**: 224–9.
- 53 Liao S, Palmer M, Fowler C *et al*. Absence of an effect of levofloxacin on warfarin pharmacokinetics and anticoagulation in male volunteers. *J Clin Pharmacol* 1996; **36**: 1072–7.
- 54 Stroud LF, Mamdani MM, Kopp A *et al*. The safety of levofloxacin in elderly patients on warfarin. *Am J Med* 2005; **118**: 1417.
- 55 Beest P-v, van Meegen E, Rosendaal FR *et al*. Drug interactions as a cause of overanticoagulation on phenprocoumon or acenocoumarol predominantly concern antibacterial drugs. *Clin Pharmacol Ther* 2001; **69**: 451–7.
- 56 Jobski K, Behr S, Garbe E. Drug interactions with phenprocoumon and the risk of serious haemorrhage: a nested case-control study in a large population-based German database. *Eur J Clin Pharmacol* 2011; **67**: 941–51.
- 57 Abbas S, Ihle P, Harder S *et al*. Risk of bleeding and antibiotic use in patients receiving continuous phenprocoumon therapy. A case-control study nested in a large insurance- and population-based German cohort. *Thromb Haemost* 2014; **111**: 912–22.
- 58 Beest P-v, Koerselman J, Herings RM. Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants. *J Thromb Haemost* 2008; **6**: 284–90.
- 59 Juurlink DN. Drug interactions with warfarin: what clinicians need to know. *CMAJ* 2007; **177**: 369–71.
- 60 Ufer M. Comparative pharmacokinetics of vitamin K antagonists—warfarin, phenprocoumon and acenocoumarol. *Clin Pharmacokinet* 2005; **44**: 1227–46.
- 61 Thachil J. The newer direct oral anticoagulants: a practical guide. *Clin Med (Lond)* 2014; **14**: 165–75.
- 62 Parasrampur DA, Mendell J, Shi M *et al*. Edoxaban drug-drug interactions with ketoconazole, erythromycin, and cyclosporine. *Br J Clin Pharmacol* 2016; **82**: 1591–600.
- 63 Gouin-Thibault I, Delavenne X, Blanchard A *et al*. Interindividual variability in dabigatran and rivaroxaban exposure: contribution of ABCB1 genetic polymorphisms and interaction with clarithromycin. *J Thromb Haemost* 2017; **15**: 273–83.
- 64 Damkier P, Hansen LL, Brosen K. Effect of diclofenac, disulfiram, itraconazole, grapefruit juice and erythromycin on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1999; **48**: 829–38.
- 65 Isohanni MH, Neuvonen PJ, Olkkola KT. Effect of erythromycin and itraconazole on the pharmacokinetics of oral lignocaine. *Pharmacol Toxicol* 1999; **84**: 143–6.
- 66 Kosoglou T, Rocci ML Jr, Vlasses PH. Trimethoprim alters the disposition of procainamide and N-acetylprocainamide. *Clin Pharmacol Ther* 1988; **44**: 467–77.
- 67 Vlasses PH, Kosoglou T, Chase SL *et al*. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. *Arch Intern Med* 1989; **149**: 1350–3.
- 68 Zapater P, Reus S, Tello A *et al*. A prospective study of the clarithromycin-digoxin interaction in elderly patients. *J Antimicrob Chemother* 2002; **50**: 601–6.
- 69 Chan AL, Wang MT, Su CY *et al*. Risk of digoxin intoxication caused by clarithromycin-digoxin interactions in heart failure patients: a population-based study. *Eur J Clin Pharmacol* 2009; **65**: 1237–43.
- 70 Tanaka H, Matsumoto K, Ueno K *et al*. Effect of clarithromycin on steady-state digoxin concentrations. *Ann Pharmacother* 2003; **37**: 178–81.

- 71 Rengelshausen J, Goggelmann C, Burhenne J *et al.* Contribution of increased oral bioavailability and reduced nonglomerular renal clearance of digoxin to the digoxin-clarithromycin interaction. *Br J Clin Pharmacol* 2003; **56**: 32–8.
- 72 Petersen P, Kastrop J, Bartram R *et al.* Digoxin-trimethoprim interaction. *Acta Med Scand* 1985; **217**: 423–7.
- 73 Bauer LA, Black DJ, Lill JS *et al.* Levofloxacin and ciprofloxacin decrease procainamide and N-acetylprocainamide renal clearances. *Antimicrob Agents Chemother* 2005; **49**: 1649–51.
- 74 Martin DE, Shen J, Griener J *et al.* Effects of ofloxacin on the pharmacokinetics and pharmacodynamics of procainamide. *J Clin Pharmacol* 1996; **36**: 85–91.
- 75 Ujhelyi MR, Bottorff MB, Schur M *et al.* Aging effects on the organic base transporter and stereoselective renal clearance. *Clin Pharmacol Ther* 1997; **62**: 117–28.
- 76 Raebel MA, Carroll NM, Andrade SE *et al.* Monitoring of drugs with a narrow therapeutic range in ambulatory care. *Am J Manag Care* 2006; **12**: 268–75.
- 77 Campbell T, Williams K. Therapeutic drug monitoring: antiarrhythmic drugs. *Br J Clin Pharmacol* 2001; **52**: 21–33.
- 78 Fost DA, Leung DY, Martin RJ *et al.* Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol* 1999; **103**: 1031–5.
- 79 Hegazy SK, Mabrouk MM, Elsis AE *et al.* Effect of clarithromycin and fluconazole on the pharmacokinetics of montelukast in human volunteers. *Eur J Clin Pharmacol* 2012; **68**: 1275–80.
- 80 Branigan TA, Robbins RA, Cady WJ *et al.* The effects of erythromycin on the absorption and disposition of kinetics of theophylline. *Eur J Clin Pharmacol* 1981; **21**: 115–20.
- 81 Reisz G, Pingleton SK, Melethil S *et al.* The effect of erythromycin on theophylline pharmacokinetics in chronic bronchitis. *Am Rev Respir Dis* 1983; **127**: 581–4.
- 82 Prince RA, Wing DS, Weinberger MM *et al.* Effect of erythromycin on theophylline kinetics. *J Allergy Clin Immunol* 1981; **68**: 427–31.
- 83 May DC, Jarboe CH, Ellenburg DT *et al.* The effects of erythromycin on theophylline elimination in normal males. *J Clin Pharmacol* 1982; **22**: 125–30.
- 84 Maddux MS, Leeds NH, Organek HW *et al.* The effect of erythromycin on theophylline pharmacokinetics at steady-state. *Chest* 1982; **81**: 563–5.
- 85 Pfeifer HJ, Greenblatt DJ, Friedman P. Effects of three antibiotics on theophylline kinetics. *Clin Pharmacol Ther* 1979; **26**: 36–40.
- 86 Carr RA, Edmonds A, Shi H *et al.* Steady-state pharmacokinetics and electrocardiographic pharmacodynamics of clarithromycin and loratadine after individual or concomitant administration. *Antimicrob Agents Chemother* 1998; **42**: 1176–80.
- 87 Brannan MD, Reidenberg P, Radwanski E *et al.* Loratadine administered concomitantly with erythromycin: pharmacokinetic and electrocardiographic evaluations. *Clin Pharmacol Ther* 1995; **58**: 269–78.
- 88 Blix HS, Viktil KK, Moger TA *et al.* Drugs with narrow therapeutic index as indicators in the risk management of hospitalised patients. *Pharm Pract (Granada)* 2010; **8**: 50–5.
- 89 Ha HR, Chen J, Freiburghaus A *et al.* Metabolism of theophylline by cDNA-expressed human cytochromes P-450. *Br J Clin Pharmacol* 1995; **39**: 321–6.
- 90 Nix DE, DeVito JM, Whitbread MA *et al.* Effect of multiple dose oral ciprofloxacin on the pharmacokinetics of theophylline and indocyanine green. *J Antimicrob Chemother* 1987; **19**: 263–9.
- 91 Wijnands WJ, Vree TB, van Herwaarden CL. The influence of quinolone derivatives on theophylline clearance. *Br J Clin Pharmacol* 1986; **22**: 677–83.
- 92 Loi CM, Parker BM, Cusack BJ *et al.* Individual and combined effects of cimetidine and ciprofloxacin on theophylline metabolism in male nonsmokers. *Br J Clin Pharmacol* 1993; **36**: 195–200.
- 93 Robson RA, Begg EJ, Atkinson HC *et al.* Comparative effects of ciprofloxacin and lomefloxacin on the oxidative metabolism of theophylline. *Br J Clin Pharmacol* 1990; **29**: 491–3.
- 94 Prince RA, Casabar E, Adair CG *et al.* Effect of quinolone antimicrobials on theophylline pharmacokinetics. *J Clin Pharmacol* 1989; **29**: 650–4.
- 95 Raoof S, Wollschlager C, Khan FA. Ciprofloxacin increases serum levels of theophylline. *Am J Med* 1987; **82**: 115–8.
- 96 Antoniou T, Gomes T, Mamdani MM *et al.* Ciprofloxacin-induced theophylline toxicity: a population-based study. *Eur J Clin Pharmacol* 2011; **67**: 521–6.
- 97 Batty KT, Davis TM, Ilett KF *et al.* The effect of ciprofloxacin on theophylline pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 1995; **39**: 305–11.
- 98 Inghammar M, Ekblom A, Engström G *et al.* COPD and the risk of tuberculosis—a population-based cohort study. *PLoS One* 2010; **5**: e10138.
- 99 Baciewicz AM, Chrisman CR, Finch CK *et al.* Update on rifampin, rifabutin, and rifapentine drug interactions. *Curr Med Res Opin* 2013; **29**: 1–12.
- 100 Wallace RJ Jr, Brown BA, Griffith DE *et al.* Reduced serum levels of clarithromycin in patients treated with multidrug regimens including rifampin or rifabutin for *Mycobacterium avium*-M. *intracellulare* infection. *J Infect Dis* 1995; **171**: 747–50.
- 101 Hafner R, Bethel J, Power M *et al.* Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother* 1998; **42**: 631–9.
- 102 Colmenero JD, Fernandez-Gallardo LC, Agundez JA *et al.* Possible implications of doxycycline-rifampin interaction for treatment of brucellosis. *Antimicrob Agents Chemother* 1994; **38**: 2798–802.
- 103 Winter HR, Trapnell CB, Slaterry JT *et al.* The effect of clarithromycin, fluconazole, and rifabutin on sulfamethoxazole hydroxylamine formation in individuals with human immunodeficiency virus infection (AACTG 283). *Clin Pharmacol Ther* 2004; **76**: 313–22.
- 104 Bhatia RS, Uppal R, Malhi R *et al.* Drug-interaction between rifampicin and cotrimoxazole in patients with tuberculosis. *Hum Exp Toxicol* 1991; **10**: 419–21.
- 105 Garske L, Kidd T, Gan R *et al.* Rifampicin and sodium fusidate reduces the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation in adults with cystic fibrosis and chronic MRSA infection. *J Hosp Infect* 2004; **56**: 208–14.
- 106 Weiner M, Burman W, Luo CC *et al.* Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother* 2007; **51**: 2861–6.
- 107 Nijland HM, Ruslami R, Suroto AJ *et al.* Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; **45**: 1001–7.
- 108 Manika K, Chatzika K, Papaioannou M *et al.* Rifampicin-moxifloxacin interaction in tuberculosis treatment: a real-life study. *Int J Tuberc Lung Dis* 2015; **19**: 1383–7.
- 109 Naidoo A, Chirehwa M, McIlleron H *et al.* Effect of rifampicin and efavirenz on moxifloxacin concentrations when co-administered in patients with drug-susceptible TB. *J Antimicrob Chemother* 2017; **72**: 1441–9.
- 110 Apseloff G, Foulds G, LaBoy-Goral L *et al.* Comparison of azithromycin and clarithromycin in their interactions with rifabutin in healthy volunteers. *Eur Respir J* 1998; **38**: 830–5.
- 111 Jordan MK, Polis MA, Kelly G *et al.* Effects of fluconazole and clarithromycin on rifabutin and 25-O-desacetyl-rifabutin pharmacokinetics. *J Clin Pharmacol* 2000; **44**: 2170–2.
- 112 Nelson MV, Berchou RC, Kareti D *et al.* Pharmacokinetic evaluation of erythromycin and caffeine administered with bromocriptine. *Clin Pharmacol Ther* 1990; **47**: 694–7.

- 113** Nakatsuka A, Nagai M, Yabe H *et al.* Effect of clarithromycin on the pharmacokinetics of cabergoline in healthy controls and in patients with Parkinson's disease. *J Pharmacol Sci* 2006; **100**: 59–64.
- 114** Perucca E. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol* 2006; **61**: 246–55.
- 115** Neuvonen PJ, Penttilä O. Interaction between doxycycline and barbiturates. *Br Med J* 1974; **1**: 535–6.
- 116** Hansen JM, Kampmann JP, Siersbaek-Nielsen K *et al.* The effect of different sulfonamides on phenytoin metabolism in man. *Acta Med Scand Suppl* 1979; **624**: 106–10.
- 117** Penttilä O, Neuvonen PJ, Aho K *et al.* Interaction between doxycycline and some antiepileptic drugs. *Br Med J* 1974; **2**: 470–2.
- 118** Shahzadi A, Javed I, Aslam B *et al.* Therapeutic effects of ciprofloxacin on the pharmacokinetics of carbamazepine in healthy adult male volunteers. *Pak J Pharm Sci* 2011; **24**: 63–8.
- 119** Antoniou T, Gomes T, Mamdani MM *et al.* Trimethoprim/sulfamethoxazole-induced phenytoin toxicity in the elderly: a population-based study. *Br J Clin Pharmacol* 2011; **71**: 544–9.
- 120** Greenberg RG, Melloni C, Wu H *et al.* Therapeutic index estimation of antiepileptic drugs: a systematic literature review approach. *Clin Neuropharmacol* 2016; **39**: 232–40.
- 121** Bialer M, Rene'H L, Perucca E. Does carbamazepine have a narrow therapeutic plasma concentration range? *Ther Drug Monit* 1998; **20**: 56–9.
- 122** Li KY, Li X, Cheng ZN *et al.* Effect of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005; **60**: 791–5.
- 123** Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozone in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; **65**: 10–20.
- 124** Farkas D, Volak LP, Harmatz JS *et al.* Short-term clarithromycin administration impairs clearance and enhances pharmacodynamic effects of trazodone but not of zolpidem. *Clin Pharmacol Ther* 2009; **85**: 644–50.
- 125** Kivisto KT, Lamberg TS, Kantola T *et al.* Plasma buspirone concentrations are greatly increased by erythromycin and itraconazole. *Clin Pharmacol Ther* 1997; **62**: 348–54.
- 126** Dean L. Diazepam therapy and CYP2C19 genotype. In: V Pratt, H McLeod, W Rubinstein *et al.*, eds. *Medical Genetics Summaries*. Bethesda, USA: National Center for Biotechnology Information, 2012. <https://www.ncbi.nlm.nih.gov/books/NBK379740/>.
- 127** Kamali F, Thomas SH, Edwards C. The influence of steady-state ciprofloxacin on the pharmacokinetics and pharmacodynamics of a single dose of diazepam in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44**: 365–7.
- 128** Fuhr U, Anders EM, Mahr G *et al.* Inhibitory potency of quinolone antibacterial agents against cytochrome P450IA2 activity in vivo and in vitro. *Antimicrob Agents Chemother* 1992; **36**: 942–8.
- 129** Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. *Eur J Clin Pharmacol* 2000; **56**: 585–9.
- 130** Meyer JM, Proctor G, Cummings MA *et al.* Ciprofloxacin and clozapine: a potentially fatal but underappreciated interaction. *Case Rep Psychiatry* 2016; **2016**: 5606098.
- 131** Nix DE, Wilton JH, Ronald B *et al.* Inhibition of norfloxacin absorption by antacids. *Antimicrob Agents Chemother* 1990; **34**: 432–5.
- 132** Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. *Clin Pharmacol Ther* 1980; **28**: 203–7.
- 133** Van Slooten AD, Nix DE, Wilton JH *et al.* Combined use of ciprofloxacin and sucralfate. *DICP* 1991; **25**: 578–82.
- 134** Parpia SH, Nix DE, Hejmanowski LG *et al.* Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; **33**: 99–102.
- 135** Lehto P, Kivisto KT. Effect of sucralfate on absorption of norfloxacin and ofloxacin. *Antimicrob Agents Chemother* 1994; **38**: 248–51.
- 136** Deppermann KM, Lode H, Hoffken G *et al.* Influence of ranitidine, pirenzepine, and aluminum magnesium hydroxide on the bioavailability of various antibiotics, including amoxicillin, cephalexin, doxycycline, and amoxicillin-clavulanic acid. *Antimicrob Agents Chemother* 1989; **33**: 1901–7.
- 137** Nix DE, Watson WA, Lener ME *et al.* Effects of aluminum and magnesium antacids and ranitidine on the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1989; **46**: 700–5.
- 138** Stass H, Bottcher MF, Ochmann K. Evaluation of the influence of antacids and H₂ antagonists on the absorption of moxifloxacin after oral administration of a 400 mg dose to healthy volunteers. *Clin Pharmacokinet* 2001; **40** Suppl 1: 39–48.
- 139** Frost RW, Lassetter KC, Noe AJ *et al.* Effects of aluminum hydroxide and calcium carbonate antacids on the bioavailability of ciprofloxacin. *Antimicrob Agents Chemother* 1992; **36**: 830–2.
- 140** Motoya T, Shimozono T, Yamaguchi T *et al.* Effects of milk and aluminum hydroxide on the absorption of norfloxacin, ciprofloxacin and tosufloxacin in healthy volunteers. *J Appl Ther* 1997; **1**: 213–7.
- 141** Nguyen VX, Nix DE, Gillikin S *et al.* Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. *Antimicrob Agents Chemother* 1989; **33**: 434–6.
- 142** Nix DE, Watson WA, Handy L *et al.* The effect of sucralfate pretreatment on the pharmacokinetics of ciprofloxacin. *Pharmacotherapy* 1989; **9**: 377–80.
- 143** Albert KS, Welch RD, DeSante KA *et al.* Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. *J Pharm Sci* 1979; **68**: 586–8.
- 144** Mapp RK, McCarthy TJ. The effect of zinc sulphate and of bicitropeptide on tetracycline absorption. *S Afr Med J* 1976; **50**: 1829–30.
- 145** Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol Mol Biol Rev* 2001; **65**: 232.
- 146** Kamberi M, Nakashima H, Ogawa K *et al.* The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; **49**: 98–103.
- 147** Miura M, Tada H, Yasui-Furukori N *et al.* Effect of clarithromycin on the enantioselective disposition of lansoprazole in relation to CYP2C19 genotypes. *Chirality* 2005; **17**: 338–44.
- 148** Crothers K, Butt AA, Gibert CL *et al.* Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* 2006; **130**: 1326–33.
- 149** Sahai J, Gallicano K, Oliveras L *et al.* Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; **53**: 292–7.
- 150** Knupp CA, Barbhuiya RH. A multiple-dose pharmacokinetic interaction study between didanosine (Videx) and ciprofloxacin (Cipro) in male subjects seropositive for HIV but asymptomatic. *Biopharm Drug Dispos* 1997; **18**: 65–77.
- 151** Grub S, Bryson H, Goggin T *et al.* The interaction of saquinavir (soft gelatin capsule) with ketoconazole, erythromycin and rifampicin: comparison of the effect in healthy volunteers and in HIV-infected patients. *Eur J Clin Pharmacol* 2001; **57**: 115–21.
- 152** Srinivas NR, Knupp CA, Batteiger B *et al.* A pharmacokinetic interaction study of didanosine coadministered with trimethoprim and/or sulphamethoxazole in HIV seropositive asymptomatic male patients. *Br J Clin Pharmacol* 1996; **41**: 207–15.
- 153** Moore KH, Yuen GJ, Raasch RH *et al.* Pharmacokinetics of lamivudine administered alone and with trimethoprim-sulfamethoxazole. *Clin Pharmacol Ther* 1996; **59**: 550–8.

- 154 Shi HY, Yan J, Zhu WH *et al.* Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. *Eur J Clin Pharmacol* 2010; **66**: 1131–6.
- 155 Sriwiriyan S, Samaeng M, Rittitid W *et al.* Pharmacokinetic interactions between ciprofloxacin and itraconazole in healthy male volunteers. *Biopharm Drug Dispos* 2011; **32**: 168–74.
- 156 Olkkola KT, Aranko K, Luurila H *et al.* A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther* 1993; **53**: 298–305.
- 157 Yeates RA, Laufen H, Zimmermann T. Interaction between midazolam and clarithromycin: comparison with azithromycin. *Int J Clin Pharmacol Ther* 1996; **34**: 400–5.
- 158 Quinney SK, Haehner BD, Rhoades MB *et al.* Interaction between midazolam and clarithromycin in the elderly. *Br J Clin Pharmacol* 2008; **65**: 98–109.
- 159 Zimmermann T, Yeates RA, Laufen H *et al.* Influence of the antibiotics erythromycin and azithromycin on the pharmacokinetics and pharmacodynamics of midazolam. *Arzneimittelforschung* 1996; **46**: 213–7.
- 160 Mattila MJ, Vanakoski J, Idanpaan HJJ. Azithromycin does not alter the effects of oral midazolam on human performance. *Eur J Clin Pharmacol* 1994; **47**: 49–52.
- 161 Hagelberg NM, Peltoniemi MA, Saari TI *et al.* Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine. *Eur J Pain* 2010; **14**: 625–9.
- 162 Backman JT, Aranko K, Himberg JJ *et al.* A pharmacokinetic interaction between roxithromycin and midazolam. *Eur J Clin Pharmacol* 1994; **46**: 551–5.
- 163 Bartkowski RR, Goldberg ME, Larijani GE *et al.* Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; **46**: 99–102.
- 164 Jokinen MJ, Olkkola KT, Ahonen J *et al.* Effect of ciprofloxacin on the pharmacokinetics of ropivacaine. *Eur J Clin Pharmacol* 2003; **58**: 653–7.
- 165 Jokinen MJ, Ahonen J, Neuvonen PJ *et al.* Effect of clarithromycin and itraconazole on the pharmacokinetics of ropivacaine. *Pharmacol Toxicol* 2001; **88**: 187–91.
- 166 Jokinen MJ, Ahonen J, Neuvonen PJ *et al.* The effect of erythromycin, fluvoxamine, and their combination on the pharmacokinetics of ropivacaine. *Anesth Analg* 2000; **91**: 1207–12.
- 167 Liukas A, Hagelberg NM, Kuusniemi K *et al.* Inhibition of cytochrome P450 3A by clarithromycin uniformly affects the pharmacokinetics and pharmacodynamics of oxycodone in young and elderly volunteers. *J Clin Psychopharmacol* 2011; **31**: 302–8.
- 168 Gupta SK, Bakran A, Johnson RW *et al.* Cyclosporin-erythromycin interaction in renal transplant patients. *Br J Clin Pharmacol* 1989; **27**: 475–81.
- 169 Freeman DJ, Martell R, Carruthers SG *et al.* Cyclosporin-erythromycin interaction in normal subjects. *Br J Clin Pharmacol* 1987; **23**: 776–8.
- 170 Federico S, Carrano R, Capone D *et al.* Pharmacokinetic interaction between levofloxacin and ciclosporin or tacrolimus in kidney transplant recipients—ciclosporin, tacrolimus and levofloxacin in renal transplantation. *Clin Pharmacokinet* 2006; **45**: 169–75.
- 171 Wrishko RE, Levine M, Primmatt DR *et al.* Investigation of a possible interaction between ciprofloxacin and cyclosporine in renal transplant patients. *Transplantation* 1997; **64**: 996–9.
- 172 Tan KK, Trull AK, Shawket S. Co-administration of ciprofloxacin and cyclosporin: lack of evidence for a pharmacokinetic interaction. *Br J Clin Pharmacol* 1989; **28**: 185–7.
- 173 Hedaya MA, El-Afify DR, El-Maghraby GM. The effect of ciprofloxacin and clarithromycin on sildenafil oral bioavailability in human volunteers. *Biopharm Drug Dispos* 2006; **27**: 103–10.
- 174 Muirhead GJ, Faulkner S, Harness JA *et al.* The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br J Clin Pharmacol* 2002; **53** Suppl 1: 37S–43S.
- 175 Shinde DD, Kim HS, Choi JS *et al.* Different effects of clopidogrel and clarithromycin on the enantioselective pharmacokinetics of sibutramine and its active metabolites in healthy subjects. *J Clin Pharmacol* 2013; **53**: 550–8.
- 176 Pan W, Bae SK, Shim EJ *et al.* Effects of clopidogrel and clarithromycin on the disposition of sibutramine and its active metabolites M1 and M2 in relation to CYP2B6*6 polymorphism. *Xenobiotica* 2013; **43**: 211–8.
- 177 Bassi PU, Onyeji CO, Ukonmwan OE. Effects of tetracycline on the pharmacokinetics of halofantrine in healthy volunteers. *Br J Clin Pharmacol* 2004; **58**: 52–5.
- 178 Pohl O, Osterloh I, Gotteland JP. Effects of erythromycin at steady-state concentrations on the pharmacokinetics of ulipristal acetate. *J Clin Pharm Ther* 2013; **38**: 512–7.
- 179 Yano R, Tani D, Watanabe K *et al.* Evaluation of potential interaction between vinorelbine and clarithromycin. *Ann Pharmacother* 2009; **43**: 453–8.
- 180 Terkeltaub RA, Furst DE, Digiacinto JL *et al.* Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 2011; **63**: 2226–37.
- 181 Kovarik JM, Beyer D, Bizot MN *et al.* Effect of multiple-dose erythromycin on everolimus pharmacokinetics. *Eur J Clin Pharmacol* 2005; **61**: 35–8.
- 182 Kovarik JM, Hsu CH, McMahon L *et al.* Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedication. *Clin Pharmacol Ther* 2001; **70**: 247–54.
- 183 Granfors MT, Backman JT, Neuvonen M *et al.* Ciprofloxacin greatly increases concentrations and hypotensive effect of tizanidine by inhibiting its cytochrome P450 1A2-mediated presystemic metabolism. *Clin Pharmacol Ther* 2004; **76**: 598–606.
- 184 Tan KK, Allwood MC, Shawket S. Effect of ciprofloxacin on the pharmacokinetics of antipyrine in healthy volunteers. *J Clin Pharm Ther* 1990; **15**: 151–4.
- 185 Ludwig E, Szekely E, Csiba A *et al.* The effect of ciprofloxacin on antipyrine metabolism. *J Antimicrob Chemother* 1988; **22**: 61–7.
- 186 Kamali F, Huang ML. Increased systemic availability of loperamide after oral administration of loperamide and loperamide oxide with cotrimoxazole. *Br J Clin Pharmacol* 1996; **41**: 125–8.
- 187 Lee BL, Medina I, Benowitz NL *et al.* Dapsone, trimethoprim, and sulfamethoxazole plasma levels during treatment of pneumocystis pneumonia in patients with the acquired immunodeficiency syndrome (AIDS). Evidence of drug interactions. *Ann Intern Med* 1989; **110**: 606–11.
- 188 Piccolo ML, Toossi Z, Goldman M. Effect of coadministration of a nutritional supplement on ciprofloxacin absorption. *Am J Hosp Pharm* 1994; **51**: 2697–9.
- 189 Penttilä O, Hurme H, Neuvonen PJ. Effect of zinc sulphate on the absorption of tetracycline and doxycycline in man. *Eur J Clin Pharmacol* 1975; **9**: 131–4.
- 190 Kays MB, Overholser BR, Mueller BA *et al.* Effects of sevelamer hydrochloride and calcium acetate on the oral bioavailability of ciprofloxacin. *Am J Kidney Dis* 2003; **42**: 1253–9.
- 191 Kato R, Ueno K, Imano H *et al.* Impairment of ciprofloxacin absorption by calcium polycarboxylate. *J Clin Pharmacol* 2002; **42**: 806–11.
- 192 Lesko LJ, Offman E, Brew CT *et al.* Evaluation of the potential for drug interactions with patiromer in healthy volunteers. *J Cardiovasc Pharmacol Ther* 2017; **22**: 434–46.
- 193 How PP, Fischer JH, Arruda JA *et al.* Effects of lanthanum carbonate on the absorption and oral bioavailability of ciprofloxacin. *Clin J Am Soc Nephrol* 2007; **2**: 1235–40.

- 194** Landersdorfer CB, Kirkpatrick CM, Kinzig M *et al.* Competitive inhibition of renal tubular secretion of ciprofloxacin and metabolite by probenecid. *Br J Clin Pharmacol* 2010; **69**: 167–78.
- 195** Jaehde U, Sorgel F, Reiter A *et al.* Effect of probenecid on the distribution and elimination of ciprofloxacin in humans. *Clin Pharmacol Ther* 1995; **58**: 532–41.
- 196** Bolhuis MS, van Altena R, van Soolingen D *et al.* Clarithromycin increases linezolid exposure in multidrug-resistant tuberculosis patients. *Eur Respir J* 2013; **42**: 1614–21.
- 197** Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol* 2000; **49**: 303–12.
- 198** Dickinson BD, Altman RD, Nielsen NH *et al.* Drug interactions between oral contraceptives and antibiotics. *Obstet Gynecol* 2001; **98**: 853–60.
- 199** Taylor J, Pemberton MN. Antibiotics and oral contraceptives: new considerations for dental practice. *Br Dent J* 2012; **212**: 481–3.
- 200** Albert RK, Schuller JL, Network C. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014; **189**: 1173–80.
- 201** Tabibian JH, Gutierrez MA. Doxycycline-induced pseudotumor cerebri. *South Med J* 2009; **102**: 310–1.
- 202** Berger FA, Monadian N, Groot N *et al.* QTc prolongation during ciprofloxacin and fluconazole combination therapy: prevalence and associated risk factors. *Br J Clin Pharmacol* 2018; **84**: 369–78.
- 203** Baxter K, Preston C. *Stockley's Drug Interactions*. London: Pharmaceutical Press, 2010.
- 204** Siedlik PH, Olson SC, Yang BB *et al.* Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; **39**: 501–4.
- 205** Ericsson CD, Feldman S, Pickering LK *et al.* Influence of subsalicylate bismuth on absorption of doxycycline. *JAMA* 1982; **247**: 2266–7.
- 206** Markert C, Schweizer Y, Hellwig R *et al.* Clarithromycin substantially increases steady-state bosentan exposure in healthy volunteers. *Br J Clin Pharmacol* 2014; **77**: 141–8.
- 207** Markert C, Hellwig R, Burhenne J *et al.* Interaction of ambrisentan with clarithromycin and its modulation by polymorphic SLCO1B1. *Eur J Clin Pharmacol* 2013; **69**: 1785–93.
- 208** Tokairin T, Fukasawa T, Yasui-Furukori N *et al.* Inhibition of the metabolism of brotizolam by erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in brotizolam metabolism. *Br J Clin Pharmacol* 2005; **60**: 172–5.
- 209** Phillips JP, Antal EJ, Smith RB. A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol* 1986; **6**: 297–9.
- 210** Aranko K, Luurila H, Backman JT *et al.* The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; **38**: 363–7.
- 211** Vlastakis L, Popa A, Neag M *et al.* Pharmacokinetic interaction between zolpidem and ciprofloxacin in healthy volunteers. *Eur J Drug Metab Pharmacokinet* 2011; **35**: 83–7.
- 212** Polk RE, Healy DP, Sahai J *et al.* Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. *Antimicrob Agents Chemother* 1989; **33**: 1841–4.
- 213** Kara M, Hasinoff BB, McKay DW *et al.* Clinical and chemical interactions between iron preparations and ciprofloxacin. *Br J Clin Pharmacol* 1991; **31**: 257–61.
- 214** Lehto P, Kivisto KT, Neuvonen PJ. The effect of ferrous sulphate on the absorption of norfloxacin, ciprofloxacin and ofloxacin. *Br J Clin Pharmacol* 1994; **37**: 82–5.
- 215** Gothoni G, Neuvonen PJ, Mattila M *et al.* Iron-tetracycline interaction: effect of time interval between the drugs. *Acta Med Scand* 1972; **191**: 409–11.
- 216** Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. Effect of food, milk, and iron. *J Am Acad Dermatol* 1985; **12**: 308–12.
- 217** Neuvonen PJ, Penttilä O. Effect of oral ferrous sulphate on the half-life of doxycycline in man. *Eur J Clin Pharmacol* 1974; **7**: 361–3.
- 218** Neuvonen PJ, Turakka H. Inhibitory effect of various iron salts on the absorption of tetracycline in man. *Eur J Clin Pharmacol* 1974; **7**: 357–60.
- 219** Venho VM, Salonen RO, Mattila MJ. Modification of the pharmacokinetics of doxycycline in man by ferrous sulphate or charcoal. *Eur J Clin Pharmacol* 1978; **14**: 277–80.
- 220** Stass H, Kubitz D. Effects of iron supplements on the oral bioavailability of moxifloxacin, a novel 8-methoxyfluoroquinolone, in humans. *Clin Pharmacokinet* 2001; **40** Suppl 1: 57–62.
- 221** Cheng SH, White A. Effect of orally administered neomycin on the absorption of penicillin V. *N Engl J Med* 1962; **267**: 1296–7.